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Breakpoints and Drug Exposure Are Inevitably Closely Linked

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It was with great interest that we read the article by Gumbo and colleagues titled “Redefining Multidrug-Resistant Tuberculosis Based on Clinical Response to Combination Therapy” (1). The authors performed a classification and regression tree (CART) analysis showing that MIC cutoff values above which therapy failure was observed are significantly lower than current breakpoints for isoniazid (INH) and rifampin (RIF). The consequence of the finding might be that the rate of multidrug-resistant tuberculosis (MDR TB) is much higher than previously assumed (1).

The impact to revise the definition of MDR TB based on these new critical concentrations will not only be statistical. Many patients will receive a second-line treatment regimen for at least 20 months that will be accompanied by a budget impact based on direct and indirect medical costs. The clinical outcome for these “new” MDR TB patients who will be treated with a second-line treatment regimen of drugs with unclear efficacy and more toxicity (2) needs to be established.

As the authors point out correctly, the identification of breakpoints should be a pharmacokinetics-pharmacodynamics (PK/PD)-derived calculation. The CART analysis showed cutoff MIC values lower than the current breakpoint MICs. The authors choose to adopt these values to distinguish between patients that would show a favorable result on first-line treatment and those who would likely fail on treatment. Alternatively, the authors could also have chosen to increase the doses of INH and RIF. This would have resulted in the same PK/PD indices and would reduce the potential increase in the number of patients labeled as MDR TB, thereby avoiding the inevitable consequence of starting a second-line treatment regimen. Increasing the doses of INH and RIF can be advocated based on *in vitro* and *in vivo* infection models showing that higher concentrations result in better outcome (3, 4). For RIF, it is already known that the current dose of 600 mg once daily is at the low end of the concentration-effect curve (5). Higher doses of RIF have even been evaluated in a randomized controlled trial to potentially shorten TB treatment (6); high doses of INH have been evaluated in the Bangladesh regimen (2). Both drugs appeared to be well tolerated. So instead of reducing the denominator of the PK/PD equation, we advocate increasing the numerator, likely resulting in the same clinical cure rate, thereby avoiding the increase of MDR TB and subsequent prolonged and toxic treatment.

We realize that our proposed strategy will likely also have a major impact on the current first-line treatment. A randomized study would ultimately be needed to compare clinical outcomes between standard treatment and treatment with high-dose INH and RIF. The publication of Gumbo and coworkers once again showed that new dosing strategies with currently available drugs are urgently needed to turn the tide of the MDR TB epidemic. It becomes clearer every day that drug susceptibility was and is important to be able to select an appropriate MDR TB treatment

regimen (7) and in addition tailor treatment further by optimizing drug exposure in patients (8).

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